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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,928	01/21/2005	Ajay S Bhatnagar	ON/4 - 32602A	6202

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
JAVANMARD, SAHAR	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
05/13/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,928	BHATNAGAR ET AL.	
	Examiner	Art Unit	
	SAHAR JAVANMARD	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,10,18,19 and 22-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 10, 18, 19, and 22-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

This Office Action is in response to applicant's arguments filed on 2/5/2008. Claim(s) 1, 10, 18, 19, and 22-24 are pending and are examined herein.

Response to Arguments

Applicant's amendments, with respect to claims 2 and 3, have rendered the 112 1st rejection moot and is hereby withdrawn.

Applicant's amendments, with respect to the 112 1st rejection of claims 18-25, as it applies to the removal of the term "prevention", have been considered and is hereby withdrawn. Examiner respectfully notes that claims 1 and 10 were inadvertently neglected in this rejection in the previous office action. Claims 1 and 10 are now rejected under the 112 1st rejection in the office action that follows below.

Applicant's amendments, with respect to claims 2 and 3, have rendered the 112 2nd rejection moot and is hereby withdrawn.

Applicant's amendments, with respect to claims 9, 11, 12, 14-16, 20, and 25 have rendered the 102 (b) rejection over Freyer et al. (European Journal of Internal Medicine, 2000) moot and is hereby withdrawn.

Applicant's arguments with respect to the 102(b) rejection of claims 10, 18, 19, and 24 over Freyer et al. (European Journal of Internal Medicine, 2000) have been fully considered but not found persuasive as Applicant is now arguing based on amended claims. Since Applicant has amended the claims, said rejection is hereby withdrawn.

Applicant's arguments with respect to claims 1 and 22-23 rejected under the 103(a) obviousness rejection as being unpatentable over Freyer et al. (European Journal of Internal Medicine, 2000) in view of Reid (N. Engl. J. Med., 2002) and Iqbal (Expert Opin. Pharmacother.), have been fully considered but found not persuasive.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In view of Applicant's amendments, the 103(a) obviousness rejection of the last Office Action has been maintained for reasons of record and modified below as a result of Applicant's claim amendments.

Applicant's arguments with respect to claim 10 rejected under the 103(a) obviousness rejection as being unpatentable over Freyer et al. (European Journal of Internal Medicine, 2000) in view of Remington's: The Science and Practice of Pharmacy, Nineteenth Edition, Vol I, 1985, page 806), have been fully considered but

found not persuasive. In view of Applicant's amendments, the 103(a) obviousness rejection of the last Office Action has been maintained for reasons of record and modified below as a result of Applicant's claim amendments.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 10 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the treatment of bone loss in patients suffering from an estrogen dependent disorder, does not reasonably provide enablement for the prevention of bone loss as recited in these claims.

The instant claims are drawn to a pharmaceutical composition and a method for the prevention of bone loss. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of

working examples; and (8) the quantity of experimentation necessary.

Nature of the invention:

The instant invention pertains to a method for the prevention of bone loss.

The state of the prior art:

The skilled artisan would view that the prevention of one or more symptoms of bone loss totally, absolutely, or permanently, is highly unlikely, since one cannot guarantee that bone loss will always be prevented.

The relative skill of those in the art:

The relative skill of those in the art is very high.

The predictability or lack thereof in the art:

The skilled artisan would view that the treatment to prevent bone loss, absolutely, or permanently is highly unpredictable.

The amount of direction or guidance presented and the presence or absence of working examples:

In the instant case, no working examples are presented in the specification as filed showing how to prevent bone loss totally, absolutely, or permanently. Note that lack of a working example, is a critical factor to be considered, especially in a case

involving an unpredictable and undeveloped art. See MPEP 2164.

Genentech, Inc. v. Novo Nordisk, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, e.g., the amount of direction or guidance provided, absence of working examples, and the predictability of the art discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test the combination in the instant claims whether preventing bone loss totally, absolutely, or permanently.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 18, 19, 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freyer et al. in view of Reid (N. Engl. J. Med., 2002) and Iqbal (Expert Opin. Pharmacother.).

Freyer discloses a study whereby patients with bone marrow involvement (BMI), common in metastatic breast cancer, and panycytopenia are administered a combination regimen including hormone therapy (i.e., anti-estrogens, LH-RH agonists, aromatase inhibitors (anastrozole), and progestin derivatives), repeated low dose chemotherapy, and bisphosphonates (pamidronate) (page 329-330, Introduction; page 331, see Treatment Strategy).

Freyer further teaches that among the five patients treated, three of them were post-menopausal with bone metastasis having ER+ and/or PR+ receptors (page 330, table 1).

Freyer does not teach specifically teach zoledronic acid as the bisphosphonate or letrozole as the aromatase inhibitor. Additionally, Freyer does not teach that the bisphosphonate is administered once every six months.

Reid teaches administering in zoledronic acid to postmenopausal women with low bone density (page 654, methods). Reid further teaches that zoledronic acid is the most potent bisphosphonate that has been studied in clinical trials to date. Reid further teaches that zoledronic acid is superior to pamidronate in the treatment of cancer-related hypercalcemia. Additionally, Reid teaches that because of its high potency, only small doses are required for the inhibition of bone resorption, and long dosing intervals may be used (page 654, lines 1-6), including administering zoledronic acid at base line and again at six months (page 654, see Treatment).

Iqbal teaches that aromatase inhibitors have been found effective in treating breast cancer in postmenopausal women (page 977, lines 11-13). Iqbal further teaches among other aromatase inhibitors, anastrazole and letrozole are markedly effective in inhibiting in situ aromatase activity (page 976, see 2.1.1.1 Endrocrine effects; page 977 Table 1). Additionally, Iqbal teaches that anastrazole and letrozole have both been approved by the FDA as first-line agents for the treatment of advanced breast cancer.

Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention to have employed the administration of an aromatase inhibitor and a bisphosphonate as taught by Freyer, using specifically zoledronic acid as the bisphosphonate and letrozole as the aromatase inhibitor. The motivation to use zoledronic acid as the bisphonate to treat bone loss is provided by Reid. As noted above, Reid teaches zoledronic acid as one of the most potent bisphosphonates that has been studied in clinical trials to date. Further, Reid teaches that because of its high potency, only small doses are required for the inhibition of bone resorption, and long

dosing intervals may be used. Thus one of ordinary skill in the art is inclined to use a bisphosphonate that exhibits the highest efficacy and least number of administrations required. The motivation to use letrozole as the aromatase inhibitor is provided by Iqbal. As discussed above, Iqbal teaches letrozole as one of the first-line agents for the treatment of advanced breast cancer. It is generally common practice among one of ordinary skill in the art to select the one of the most active analogs in a family of drugs to achieve the most promising results.

Claims 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Freyer et al. in view of Reid (N. Engl. J. Med., 2002) and Iqbal (Expert Opin. Pharmacother.) as applied to claims 1, 18, 19, 22-24 above in further view of Remington's: The Science and Practice of Pharmacy, Nineteenth Edition, Vol I, 1985, page 806.

Freyer, Reid, and Iqbal are discussed above.

Neither Freyer, Reid, nor Iqbal teach packaging the combination of zoledronic acid and letrozole.

Remington teaches that the inclusion of a package insert including "indications and use" of the pharmaceutical composition is mandated by 21 CFR 201.57. The addition of printed matter in the form of instructions for use in no way depends on the kit and the kit does not effect the pharmaceutical composition. All that the printed material does is teach new use for an existing product. Where the printed matter is not

functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability. *In re* Ngai (70 USPQ2d 1862 (CA FC 2004).

Thus, it would have been obvious to one of ordinary skill in the art to have combined the aromatase inhibitor and bisphosphonate as taught by Freyer, Reid, and Iqbal and included the medication as a package with instructions. The motivation is that it is mandated by law (21 CFR 201.57).

Conclusion

Claims 1, 10, 18, 19, and 22-24 are not allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAHAR JAVANMARD whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/S. J./

Examiner, Art Unit 1617

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617